FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
228.1010	09/980727

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/03612	April 20, 2000	April 22, 1999

TITLE OF INVENTION

METHOD FOR PRODUCING A WATER-INSOLUBLE AMORPHOUS OR PARTIALLY AMORPHOUS CONTROLLED RELEASE MATRIX

APPLICANT(S) FOR DO/EO/US

REIN, Hubert; and STEFFENS, Klaus-Jurgen

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Letter Re: Priority
Postcard
Abstract on separate sheet

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/980727	PCT/EP00/03612	228-1010

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1,000.00**	
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO **$860.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**	
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**	
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
	ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**
	Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	19 - 20 =	0	x $18.00	**$0.00**
Independent claims	2 - 3 =	0	x $80.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**

TOTAL OF ABOVE CALCULATIONS =		**$890.00**
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.	☐	**$0.00**
SUBTOTAL =		**$890.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +		**$0.00**
TOTAL NATIONAL FEE =		**$890.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**	☐	**$0.00**
TOTAL FEES ENCLOSED =		**$890.00**
	Amount to be: refunded	$
	charged	$

☒ A check in the amount of **$890.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **50-0552** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Clifford M. Davidson, Esq.
DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018

23280
PATENT TRADEMARK OFFICE

SIGNATURE

Robert J. Paradiso
NAME

41,240
REGISTRATION NUMBER

October 19, 2001
DATE

228.1010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: To Be Assigned — Art Unit: Not Yet Known

Re: Application of: Hubert REIN, et al.

Serial No.: 09/980,727

Filed: April 20, 2000

For: **METHOD FOR PRODUCING A WATER-INSOLUBLE AMORPHOUS OR PARTIALLY AMORPHOUS CONTROLLED RELEASE MATRIX**

PETITION FOR EXTENSION UNDER 37 CFR 1.136(a)

May 17, 2002

Box: MISSING PARTS
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby petition the Assistant Commissioner for Patents to extend the time for responding to the Notice of Missing Requirements mailed on January 29, 2002 for two (2) months from March 29, 2002 to May 29, 2002.

Enclosed is a check for $400.00 to cover the extension fee.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Cary S. Kappel
Reg No. 36,561

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

I hereby certify that this correspondence and/or documents and/or fee referred to as attached therein are being deposited with the United States Postal Service as "first class mail" in an envelope addressed to "Assistant Commissioner for Patents, Washington, D.C. 20231" on May 17, 2002.
DAVIDSON, DAVIDSON & KAPPEL, LLC
BY: Randolph McQueen

228.1010

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	REIN, Hubert et al.
	Serial No.:	To Be Assigned
	Filed:	Simultaneously Herewith
	For:	**METHOD FOR PRODUCING A WATER-INSOLUBLE AMORPHOUS OR PARTIALLY AMORPHOUS CONTROLLED RELEASE MATRIX**

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231
BOX: PATENT APPLICATION

October 19, 2001

Sir:

Please amend the above-identified application as follows:

IN THE SPECIFICATION

Please add the enclosed abstract to the application as page number 16.

IN THE CLAIMS.

Please **amend** the claims as follows:

"Express Mail" mailing label no. EL 914492636US.
Date of deposit: October 19, 2001.
I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the indicated date above in an envelope addressed to: "Assistant Commissioner for Patents, Washington, D.C. 20231".
DAVIDSON, DAVIDSON & KAPPEL, LLC
BY: _____

3. (Amended) Method according to claim 1, characterized in that, the matrix is amorphous or partially amorphous.

4. (Amended) Method according to claim 1, characterized in that, the polysaccharide is starch or a derivative thereof.

5. (Amended) Method according to claim 1, characterized in that, the matrix is water-soluble.

6. (Amended) Method according to claim 1, characterized in that, the matrix is a controlled release matrix.

7. (Amended) Method according to claim 1, characterized in that, the release of the active agent of the dosage form substantially follows the lapidus function.

8. (Amended) Method according to claim 1, characterized in that, the release of the active agent of the dosage form may be adjusted over 24 hours or more.

9. (Amended) Method according to claim 1, characterized in that, at least one pharmaceutically active agent is present in the matrix in dissolved, solid or liquid form.

12. (Amended) Dosage form according to claim 10, characterized in that, the matrix is amorphous or partially amorphous.

13. (Amended) Dosage form according to claims 10, characterized in that, the polysaccharide is starch or a derivative thereof.

14. (Amended) Dosage form according to claim 10, characterized in that, the matrix is water-insoluble.

15. (Amended) Dosage form according to claim 10, characterized in that, the matrix is a controlled release matrix.

16. (Amended) Dosage form according to claim 10, characterized in that, the release of the active agent substantially follows the lapidus function.

17. (Amended) Dosage form according to claim 10, characterized in that, the release of the active agent is adjusted over a period of up to 24 hours or longer.

18. (Amended) Dosage form according to claim 10, characterized in that, at least one pharmaceutically active agent is present in the matrix in dissolved, solid or liquid form.

19. (Amended) Use of a dosage form according to claim 10 for producing granulates for tabletting the filling capsules, for further processing using injection molding techniques, as an adjuvant for direct tabletting and/or for producing mono-block pharmaceutical dosage forms.

REMARKS

Initially, the Examiner is requested to examine the claims as amended under PCT Article 34. A clean copy of these claims are attached herewith.

Further, claims 3-9 and 12-19 have been amended herewith to remove the multiple dependencies present in these claims. No new matter has been added by virtue of this amendment.

228.1010

Applicants believe that claims, as presented, are in condition for allowance. An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Robert J. Paradiso
Reg. No. 41,240

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485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

International PCT Application No. PCT/EP00/03612

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims have been amended as follows:

3. (Amended) Method according to claim 1 [or claim 2] , characterized in that, the matrix is amorphous or partially amorphous.

4. (Amended) Method according claim 1 [to any one of the preceeding claims] , characterized in that, the polysaccharide is starch or a derivative thereof.

5. (Amended) Method according claim 1 [to any one of the preceding claims], characterized in that, the matrix is water-soluble.

6. (Amended) Method according to claim 1 [according to any one of the preceding claims] , characterized in that, the matrix is a controlled release matrix.

7. (Amended) Method according to claim 1 [any one of the preceding claims], characterized in that, the release of the active agent of the dosage form substantially follows the lapidus function.

8. (Amended) Method according to claim 1 [any one of the preceding claims], characterized in that, the release of the active agent of the dosage form may be adjusted over 24 hours or more.

9. (Amended) Method according to claim 1 [any one of the preceding claims], characterized in that, at least one pharmaceutically active agent is present in the matrix in dissolved, solid or liquid form.

12. (Amended) Dosage form according to claim 10 [or claim 11], characterized in that, the matrix is amorphous or partially amorphous.

13. (Amended) Dosage form according to claim 10 [any one of claims 10 to 12], characterized in that, the polysaccharide is starch or a derivative thereof.

14. (Amended) Dosage form according to claim 10 [any one of claims 10 to 13], characterized in that, the matrix is water-insoluble.

15. (Amended) Dosage form according to claim 10 [any one of claims 10 to 14] , characterized in that, the matrix is a controlled release matrix.

16. (Amended) Dosage form according to claim 10 [any one of claims 10 to 15], characterized in that, the release of the active agent substantially follows the lapidus function.

17. (Amended) Dosage form according to claim 10 [any one of claims 10 to 16], characterized in that, the release of the active agent is adjusted over a period of up to 24 hours or longer.

18. (Amended) Dosage form according to claim 10 [any one of claims 10 to 17], characterized in that, at least one pharmaceutically active agent is present in the matrix in dissolved, solid or liquid form.

19. (Amended) Use of a dosage form according to claim 10 [to 18] for producing granulates for tabletting the filling capsules, for further processing using injection molding techniques, as an adjuvant for direct tabletting and/or for producing mono-block pharmaceutical dosage forms.

6/pts

Method for producing a water-insoluble amorphous or partially amorphous controlled-release matrix

The invention relates to a method for producing pharmaceutical dosage forms or precursors thereof by means of extrusion.

The invention further relates to a pharmaceutical dosage form which may be produced by means of extrusion methods.

Extrusion is a widespread process, especially in the adhesive industry or in plastics processing for modifying polysaccharides, in particular starches. Extrusion is known in food technology for the production of starch-containing compositions, such as noodles, so-called peanut flips or various sweets. However, the production conditions of all of these products are selected in such a way that foamed, so-called popped products are obtained.

In pharmaceutical technology extrusion is used for the processing of waxes, fatty alcohols, fats and various thermoplastics and duroplastics. For example, extruded matrices from various polymer compounds are disclosed in EP-A2 0 240 904, EP-A2 0 240 906 and EP-A2 0 358 105. The processing of starch-containing mixtures into pharmaceutical products (capsules) by means of an injection-molding technique is described in EP-B2 0 118 240. In this context, it is not so well known how the polysaccharides used change during extrusion.

Extrusion methods for producing solid dispersions of an active agent in a polymeric carrier are known from EP-A 0 580 860. Among the raw materials which may be used are starch and starch derivatives mentioned in general. However, the method described therein is not suitable for preparations having starch as the main ingredient.

WM:NH:aw

In pharmaceutical technology, orally administered dosage forms such as, for example, tablets, dragées or capsules are by far the most important. These also include the so-called controlled release (retard) dosage forms, which contain a relatively high dose of active agent and release this active agent in a controlled manner over a longer period of time. For the patient, this means that the frequency of medication can be significantly reduced. From a medical-pharmacological point of view, the advantage of the controlled release dosage forms lies in a very uniform concentration of the active agent in the blood, producing a long-lasting effect with less side effects. When formulating controlled release dosage forms, the so-called matrix form is of fundamental importance. Matrix means a shaped body, such as, for example, a tablet or dragée made of inert adjuvants, which release the active agents into the gastro-intestinal tract in a controlled manner. The release of the active agent generally occurs partly by diffusion, partly by slow degradation of the matrix.

In pharmaceutical technology such matrices are produced from synthetic polymers, such as polyacrylate or polyethylene. In this context, extrusion methods for the production of controlled-release forms from synthetic raw materials are also known.

One fundamental disadvantage of dosage forms produced hitherto by means of extrusion methods is the use of excipients such as plastics, waxes or even fatty alcohols. These adjuvants, which are not biologically degradable and in part environmentally harmful, such as residual monomers in the polymers used, are even up to the present day indispensable for dosage forms produced by means of extrusion methods and allowing a controlled and slow release of the active agent. Moreover, there is no known extrusion method for the production of dosage forms which allow a rapid release of the active agent.

There is thus a great need for the provision of an extrusion method for the production of dosage forms having regulated, i.e. by choice delayed or even a more rapid release of the active agent, which overcomes the disadvantages of the prior art, and which particularly

avoids the use of biologically non-degradable and to some extent even environmentally toxic excipients. Further objects can be gathered from the following description of the invention.

The solution of the objects relating to the method lies in the combination of features of claim 1.

Advantageous embodiments of the inventive method are defined in themethod sub-claims.

According to the invention a method for producing of dosage forms or precursors thereof by means of extrusion is suggested, characterized in that the dosage form has a matrix which essentially comprises the active agent content, the essential features of which matrix are formed by the extrusion, and which comprises a biologically degradable polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as a constituent of the matrix and at least one pharmaceutically effective substance.

According to a preferred embodiment, the release of the active agent of the dosage form is regulated by the addition of adjuvants and/or by variation of the extrusion process parameters, such as temperature, geometry of the dies and/or the extrusion speed.

In a further preferred embodiment the matrix of the dosage form made according to the invention is amorphous or partially amorphous.

Furthermore, the invention in a preferred embodiment relates to a method, wherein the dosage form according to the invention comprises in the matrix starch or a derivative thereof, in particular amorphous or partially amorphous starch or a derivative thereof, as the polysaccharide.

In a further preferred embodiment the invention relates to a method of production wherein the dosage form comprises a water-insoluble and preferably a swellable matrix.

According to an especially preferred embodiment, the dosage form according to the invention is a controlled release matrix.

Further preferred embodiments include a dosage form according to the invention showing a release of the active agent which essentially follows the lapidus function and which especially preferred shows a release of the active agent which is adjustable over 24 hours or longer.

A further essential object of the invention lies in the provision of a dosage form which essentially can function without biologically degradable ingredients.

According to the invention, this object is solved by a dosage form comprising a matrix in which the active agent is essentially contained, and whose essential properties are determined by the extrusion process and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as an essential constituent of the matrix, and at least one pharmaceutically effective substance.

Furthermore, the invention relates to the use of the inventive dosage form as adjuvant in direct tabletting, for producing granulates for tabletting and capsule-filling, for further processing using injection molding techniques and/or for producing mono-block pharmaceutical dosage forms.

During the extrusion process, i.e. while using or applying heat, shear forces and pressure, an amorphous or partially amorphous matrix is generated from the crystalline or partly crystalline polysaccharides, in particular from starch or derivatives thereof, or from mixtures

of these components. For the reproducible production of dosage forms based on the extrusion of polysaccharides and derivatives thereof, the extrusion conditions, such as temperature, die geometry and extrusion speed, are very important. For example, native starch may be completed plastified or vitrified under suitable extrusion conditions, so that homogeneous plastic-like shaped bodies are obtained.

When extruding starch, heating is only necessary at the beginning of the process. In the further course of the process, the heat generated by the strong shear and friction is preferably eliminated by cooling, in order to maintain a constant temperature. The formulations used in the inventive method are comprised of a mixture of polysaccharides and/or derivatives thereof, preferably of a mixture of starch and/or starch derivatives, there being various types of starch which are suitable. Furthermore, the mixture contains at least one pharmaceutically effective substance in an amount of up to 50% and preferably of up to 30%, based on the total weight of the formulation, and may additionally comprise further different substances. Water in concentrations of up to 15% should be added to the thoroughly mixed dry formulation. Where a forced conveying extruder is used, a lesser water content than 15% is sufficient.

After thoroughly mixing and the addition of water the obtained pre-blend should preferably be screened so that it is free of lumps, in order to ensure perfect conveyance through the screw feeder. Starting and cleaning of the extruder may for example be carried out using corn grit. When generating a matrix according to the inventive method, the temperature at the orifice of the extruder should not exceed 100°C under normal pressure, since at temperatures above 100°C the formation of a matrix free of pores will hardly be possible. The total energy fed into the process, in the form of shear forces, temperature, heat or pressure, should be as constant as possible and should be sufficient to achieve glass transition. The optimal screw speed and geometry of dies may be adjusted to the mixture comprised of the inventive carrier and water. At extrusion temperatures below 100°C and suitable screw speeds transparent and

completely amorphous products are obtained in most cases. The degree of plastification of the active agent/polysaccharide mixture and preferably of the active agent/starch mixtures is closely linked to the screw speed. While extrusion is no longer possible below the lowest speed, a screw speed which is too high causes the dosage form to "pop open".

Varying the extrusion process parameters allows the production of dosage forms according to the inventive method which show regulated release of the active agent. Within the meaning of the present invention "regulated" means that by the inventive extrusion method dosage forms with rapid as well as dosage forms with delayed release, so-called controlled-release dosage forms with release periods of up to 24 hours or longer, may be produced. Besides the process parameters already mentioned, also the processing temperature is of major importance in relation to the regulation of the release of the active agent. Dosage forms with rapid release may be obtained for example by extrusion below the temperature of gelatinisation of the polysaccharides used in each case. Since, among other things the density of the matrix influences the release of the incorporated active agents, corresponding dosage forms with controlled release may be produced by partial to complete vitrification, i.e. by transition into the amorphous state of the polysaccharide-containing mixture under suitable extrusion conditions. In contrast to previously described systems, such an amorphous or partially amorphous matrix according to the inventive method, which preferably is made of amorphous or partially amorphous starch or derivatives thereof or of mixtures of these components, is essentially not water-soluble, but instead preferably swellable and water-insoluble. The pharmaceutically effective substance or substances may be present in the matrix in dissolved, solid or liquid form.

Examples of starches which may be used in the inventive production method are tapioca starch, wheat starch, potato starch, starch 1500® (partially pregelatinized corn starch, available from Colorcon), Waxylis® (wax corn starch from Roquette), Eurylon 7® (amylo corn starch available from Roquette), corn starch, acetylic starch.

In addition, dosage forms are obtainable according to the inventive extrusion method which have regulated release of the active agent due to the addition of adjuvants. For accelerating release of the active agent by formation of pores in the matrix, the following substances may be added, for example:

- hydrophilic or amphiphilic solids, water-soluble substances, such as sodium chloride, lactose, surface-active substances, such as for example sodium lauryl sulfate, silica (colloidally dispersed and/or as xerogel),
- hydrophilic or amphiphilic liquids, polyglycols, such as for example glycerol, polyethylene glycol, surface-active substances, such as for example polysorbate,
- gases, such as for example nitrogen, carbon dioxide.

A reduction in the release of the active agent by inhibiting the diffusion may for example be effected by the addition of the following adjuvants:

- lipophilic or amphiphilic adjuvants of natural, synthetic and/or partially synthetic origin, such as for example fats, fatty acids, waxes in solid or liquid state,
- saturated or unsaturated hydrocarbons,
- metal soaps, such as for example magnesium stearate.

Furthermore, a reduction in the release of the active agent may be achieved by the formation of stoichiometric or non-stoichiometric complexes, such as for example iodine-starch complex, miltefosin-amylose complex.

Moreover, the release of the incorporated active agents can be influenced by the use of suitable blends of the components of the matrix, preferably by using blends of different starches and/or derivatives thereof. Further factors which can also influence the release of the active agent are the outer surface of the shaped body of the dosage form and its particle size, or the distribution of the active agent(s) within the particle.

An examination of the course of the release of the active agent shows that the release of the active agent is preferably controlled by diffusion and follows the so-called lapidus rule, as shown in the tests described below. The course of the release does not change, even after storage of the dosage forms over several months.

The dosage forms produced according to the inventive method may be used to produce granulates for tabletting and filling capsules, may be used as adjuvants for direct tabletting, for further processing by means of extrusion molding techniques and/or as mono-block dosage forms, where the the extrudate is formed by means of a suitable arrangement at the extrusion die – similar to the case of soap production. The inventive method allows the production and use of mono-block forms, in the process of which an extrude is created that is vitrified only at the surface and includes the active substance/carrier mixture in an unchanged state in its interior. In order to achieve the desired bio-pharmaceutical properties of the dosage form, all adjuvants known for producing solid forms may be used.

Drying of the dosage form can take place merely through the frictional heat that is created, so that a final drying step is not necessary. In a production extruder, preferably a twin screw extruder, especially preferred in a forced conveying twin screw extruder, all process steps, such as dosing, moistening, mixing, extruding and forming can be carried out continuously. The inventive method is thus able to combine the processes of mixing, granulating and drying, for which no additional energy has to be expended, in one piece of equipment.

According to the invention, also the number of possible incompatibilities is reduced, since the dosage form comprises for example only one excipient, preferably starch or a derivative thereof, and one pharmaceutically effective substance. The matrix made according to the inventive method further prevents a possible unintended demixing.

The following examples show that the degree of retardation of the active agent is best regulated by the process or the process parameters, the type of polysaccharide or the addition of further adjuvants. The examples serve to illustrate the invention only and do not represent any limitations to certain embodiments or applications. Rather, further embodiments within the scope defined by the attached claims are conceivable.

Examples

In the following examples, which have been carried out according to the inventive method, various polysaccharides with the addition of caffeine as a model active agent were used. The extrusion experiments were carried out with a Brabender one-screw extruder type 811201. This device has three segments which may be tempered independently of each other, the feed area, the screw area and the die. A conveyor screw was used without compression, having a screw length of 22 cm, a screw diameter of 19 mm, a core diameter of 16 mm and a pitch of 15 mm. Dies with different diameters between 2.5 and 7 mm were used.

The batch size in the experiments was between 350 and 600 grams. Active agent and starch were thoroughly mixed in a Stephan mixer, moistened with 15% water; this pre-blend was then screened until free of lumps.

Temperatures of about 65°C in the feed area of the extruder, of about 80°C in the screw area and of about 98°C at the die have proven to be a suitable choice of temperature for carrying out the inventive method.

The proof of the transition of the crystalline or partially crystalline structures of the polysaccharides into amorphous or partially amorphous structures may be carried out with the aid of different techniques.

By means of differential scanning colorimetry (DSC) the transition of the crystalline or partially crystalline starch into the amorphous state can be detected. Under suitable extrusion conditions the starch becomes completely vitrified, i.e. changes into the amorphous state. By way of example, a test with tapioca starch as the polysaccharide and caffeine as the active agent was carried out. The thermogram of the pre-blend is shown in Fig. 1a, consisting of 90% tapioca starch and 10% caffeine with the addition of water, shows the typical endothermic peaks in the range of about 65°C.

After the extrusion carried out according to the invention, no peaks in the decisive temperature range are detectable. It has to be concluded that the starch has been completely vitrified, which means that it has turned into the amorphous state (see Fig. 1b).

The transition from the crystalline or partially crystalline into the amorphous or partially amorphous state may also be detected with the aid of x-ray diffraction. For the following exemplary test, a sample consisting of 80% potato starch and 20 caffeine was used. The x-ray diffraction pattern of the potato starch-caffeine pre-blend shown in Fig. 2 shows the signals of the crystalline part of the starch in the range of around 20°C. After application of the inventive method, the x-ray diffraction pattern of the corresponding extrudate does not have any signals anymore, which indicates a crystalline portion of the starch.

In this context it is once again pointed out that the degree of destructurization into the glass state is decisive for the kinetics of the release of the active agents. Checking of the release of the active agent was done in a paddle agitator model according to USP in the liquids of 0.1 N

hydrochloric acid (artificial gastric fluid having a pH value of 1) and in phosphate buffer pH 7.2 (artificial intestinal fluid). In this context it has again to be pointed out that the extrudates did not dissolve in the test, but merely a swelling of the extrudes was observed. In the following exemplary test to determine the quantitative release of the active agent, a sample consisting of a commercially available starch Eurylon 7® (amylo corn starch available from Roquette) and a 30% portion of caffeine was used. The diagram in Fig. 3 shows the quantitative course of the release of the active agent. For comparative purposes, the release of pure caffeine, not retarded and filled in a capsule has been drawn in.

One can see that embedding the caffeine in a polysaccharide matrix leads to a substantial delay in release, in the present case from about 15 minutes to about 8 to 10 hours for the total dose of 25 mg.

A diagram of the amount released against the square root of time according to the lapidus rule shows an almost straight lined course of the curves, which indicates that the release of the active agent is controlled by diffusion (see Fig. 4).

As already described, the release rate of the active agent may also be regulated by the kind of polysaccharide or the polysaccharide mixture. In the following example, a pre-blend consisting of potato starch and 10% caffeine was used for a quantitative investigation of the release of the active agent. Changing the type of starch, together with a lower dose of the active agent leads to a significant slowdown in the release of the active agent. The diagram shown in Fig. 5 indicates that the extrudate prepared according to the inventive method provides a release of the active agent over a period of 24 hours.

The graph shown in Fig. 6 according to lapidus rule indicates that the release of the active agent is controlled by diffusion.

As already described above, the duration and course of the total release of the active agent can be regulated. Very long active agent release times, such as 24 hours in the above-mentioned example, are regarded as advantageous in view of the development of a new retardation principle, since in such a way "reserves" for extremely good water-soluble active agents are obtained. Release of the active agent may be selectively influenced, as already described several times, by the polysaccharides or corresponding derivatives and mixtures thereof, by the addition of corresponding adjuvants and/or by the extrusion process parameters.

According to the inventive method, faster release times of the active agents may also be achieved. The table shown below shows by way of example that a process parameter change, which for example leads to an incomplete vitrification, results in the possibility of regulating the release times of the active agent over a wide range.

Table

Polysachharide	Active agent	Concentration of active agent	Period in which 50% of the active agent is released [min]	Period in which the active agent is theoretically released [hours]
Tapioca starch	Caffeine	10% (50 mg)	240	16
Tapioca starch	Caffeine	10% (50 mg)	120	8
Corn starch	Caffeine	30% (50 mg)	195	13
Corn starch	Caffeine	30% (50 mg)	55	3.7

As can be seen from this table, for identical types of starch relatively short release times of the active agent as well as release times of the active agent falling into the range of controlled release dosage forms may be achieved solely by varying the process parameters.

Claims

1. Method for producing pharmaceutical dosage forms or precursors thereof by means of extrusion,
characterized in that, the dosage form has a matrix in which the active agent is essentially contained and whose essential properties are determined by the extrusion process and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as an essential constituent, and at least one pharmaceutically effective substance.

2. Method according to claim 1,
characterized in that, the release of the active agent of the dosage form is regulated by the addition of adjuvants and/or by variation of the extrusion process parameters, such as temperature, geometry of dies and/or the extrusion speed.

3. Method according to claim 1 or claim 2,
characterized in that, the matrix is amorphous or partially amorphous.

4. Method according to any one of the preceding claims,
characterized in that, the polysaccharide is starch or a derivative thereof.

5. Method according to any one of the preceding claims,
characterized in that, the matrix is water-soluble.

6. Method according to any one of the preceding claims,
characterized in that, the matrix is a controlled release matrix.

7. Method according to any one of the preceding claims,
characterized in that, the release of the active agent of the dosage form substantially follows the lapidus function.

8. Method according to any one of the preceding claims,
characterized in that, the release of the active agent of the dosage form may be adjusted over 24 hours or more.

9. Method according to any one of the preceding claims,
characterized in that, at least one pharmaceutically effective substance is present in dissolved, solid or liquid form within the matrix.

10. Pharmaceutical dosage form, comprising a matrix in which the active agent is essentially contained and whose essential properties are determined by the extrusion process and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as the essential constituent of the matrix, and at least one pharmaceutically effective substance.

11. Dosage form according to claim 10,
characterized in that, the release of the active substance is regulated by the addition of adjuvants and/or by variation of the extrusion process parameters, such as temperature, geometry of dies and/or the extrusion speed.

12. Dosage form according to claim 10 or claim 11,
characterized in that, the matrix is amorphous or partially amorphous.

13. Dosage form according to any one of claims 10 to 12, **characterized in that,** the polysaccharide is starch or a derivative thereof.

14. Dosage form according to any one of claims 10 to 13, **characterized in that,** the matrix is water-insoluble.

15. Dosage form according to any one of claims 10 to 14, **characterized in that,** the matrix is a controlled release matrix.

16. Dosage form according to any one of claims 10 to 15, **characterized in that,** the release of the active agent substantially follows the lapidus function.

17. Dosage form according to any one of claims 10 to 16, **characterized in that,** the release of the active agent is adjusted over a period of up to 24 hours or longer.

18. Dosage form according to any one of claims 10 to 17, **characterized in that,** at least one pharmaceutically effective substance is present in dissolved, solid or liquid form within the matrix.

19. Use of a dosage form according to claim 10 to 18 for producing granulates for tabletting and filling capsules, for further processing using injection molding techniques, as an adjuvant for direct tabletting and/or for producing mono-block pharmaceutical dosage forms.

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Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: METHOD FOR PRODUCING A WATER–INSOLUBLE AMORPHOUS OR PARTIALLY AMORPHOUS CONTROLLED RELEASE MATRIX

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG EINER WASSERUNLÖSLICHEN AMORPHEN ODER TEILAMORPHEN RETARDMATRIX

(57) Abstract

The invention relates to a method for producing pharmaceutical forms or preliminary stages thereof by means of extrusion. The pharmaceutical form has a matrix in which the active agent is contained essentially, and whose essential characteristics are determined by the extrusion process and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as an essential constituent, and at least one pharmaceutically active substance. The invention also relates to a pharmaceutical form which has a matrix in which the active agent is contained essentially, and whose essential characteristics are determined by the extrusion process, and which comprises a polysaccharide and/or a derivative thereof and/or a complex thereof and/or any mixture of the aforementioned substances with other substances and/or saccharides and/or derivatives thereof as an essential constituent, and at least one pharmaceutically active substance. Finally, the invention also relates to the use of said pharmaceutical form for producing granulates for tabletting and filling capsules, for further processing using injection moulding techniques and as an auxiliary material for direct tabletting and/or for producing monobloc pharmaceutical forms.

(57) Zusammenfassung

Die Erfindung betrifft ein Verfahren zur Herstellung von Arzneiformen oder Vorstufen davon mittels Extrusion, wobei die Arzneiform eine den Wirkstoffgehalt im wesentlichen enthaltende Matrix aufweist, die in ihren wesentlichen Eigenschaften durch die Extrusion ausgebildet wird, und ein Polysaccharid und/oder ein Derivat davon und/oder einen Komplex davon und/oder eine beliebige Mischung der vorgenannten Substanzen mit anderen Substanzen und/oder Sacchariden und/oder Derivaten davon als wesentlichen Bestandteil der Matrix sowie mindestens eine pharmazeutisch wirksame Substanz umfasst. Die Erfindung betrifft weiterhin eine Arzneiform, welche eine den Wirkstoffgehalt im wesentlichen enthaltende Matrix, die in ihren wesentlichen Eigenschaften durch Extrusion ausgebildet ist, und ein Polysaccharid und/oder ein Derivat davon und/oder einen Komplex davon und/oder eine beliebige Mischung der vorgenannten Substanzen mit anderen Substanzen und/oder Sacchariden und/oder Derivaten davon als wesentlichen Bestandteil der Matrix sowie mindestens eine pharmazeutisch wirksame Substanz umfasst. Weiter betrifft die Erfindung die Verwendung der Arzneiform zur Herstellung von Granulaten für die Tablettierung und Kapselfüllung, zur Weiterverarbeitung mit Spritzgussverfahren, als Hilfsstoff bei der Direkttablettierung und/oder zur Herstellung von Monoblockarzneiformen.

DSC data of extrudable mixture made of 90% tapioca starch and 10% caffeine

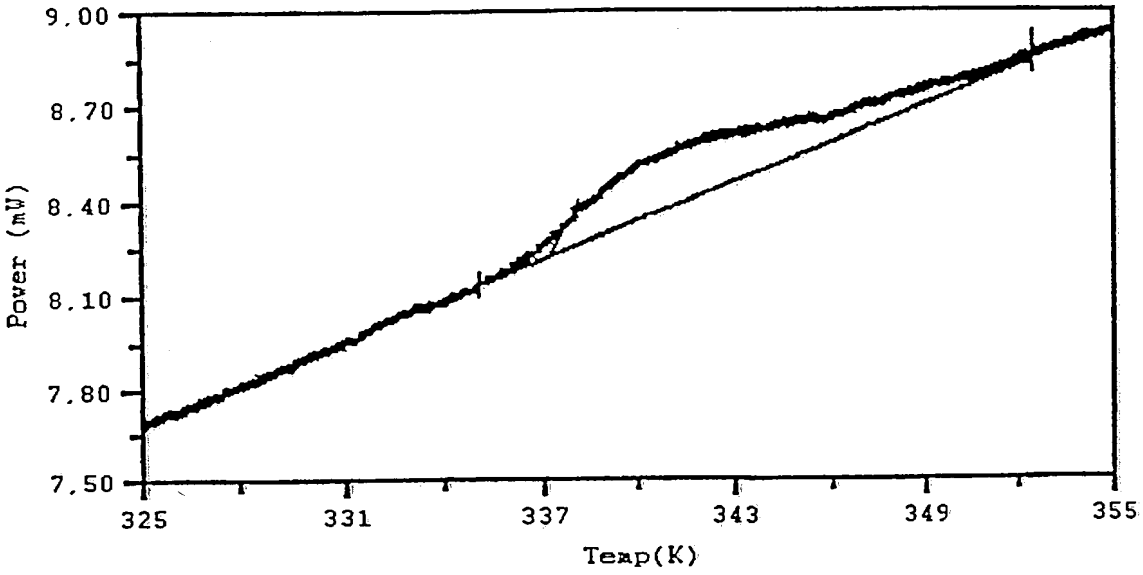


Fig. 1a

DSC data of the extrudate made of 90% tapioca starch and 10% caffeine

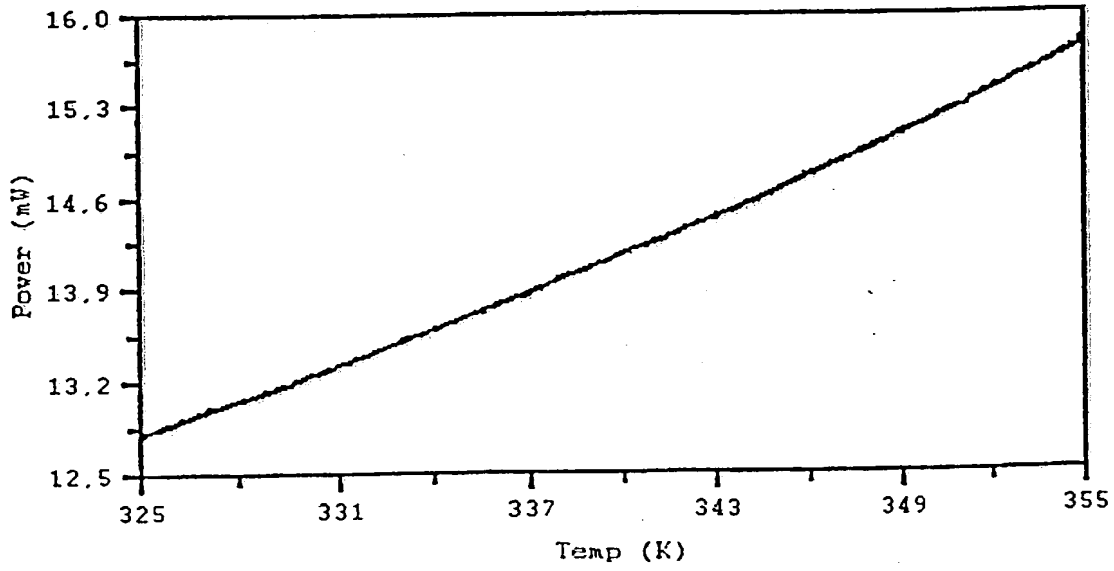
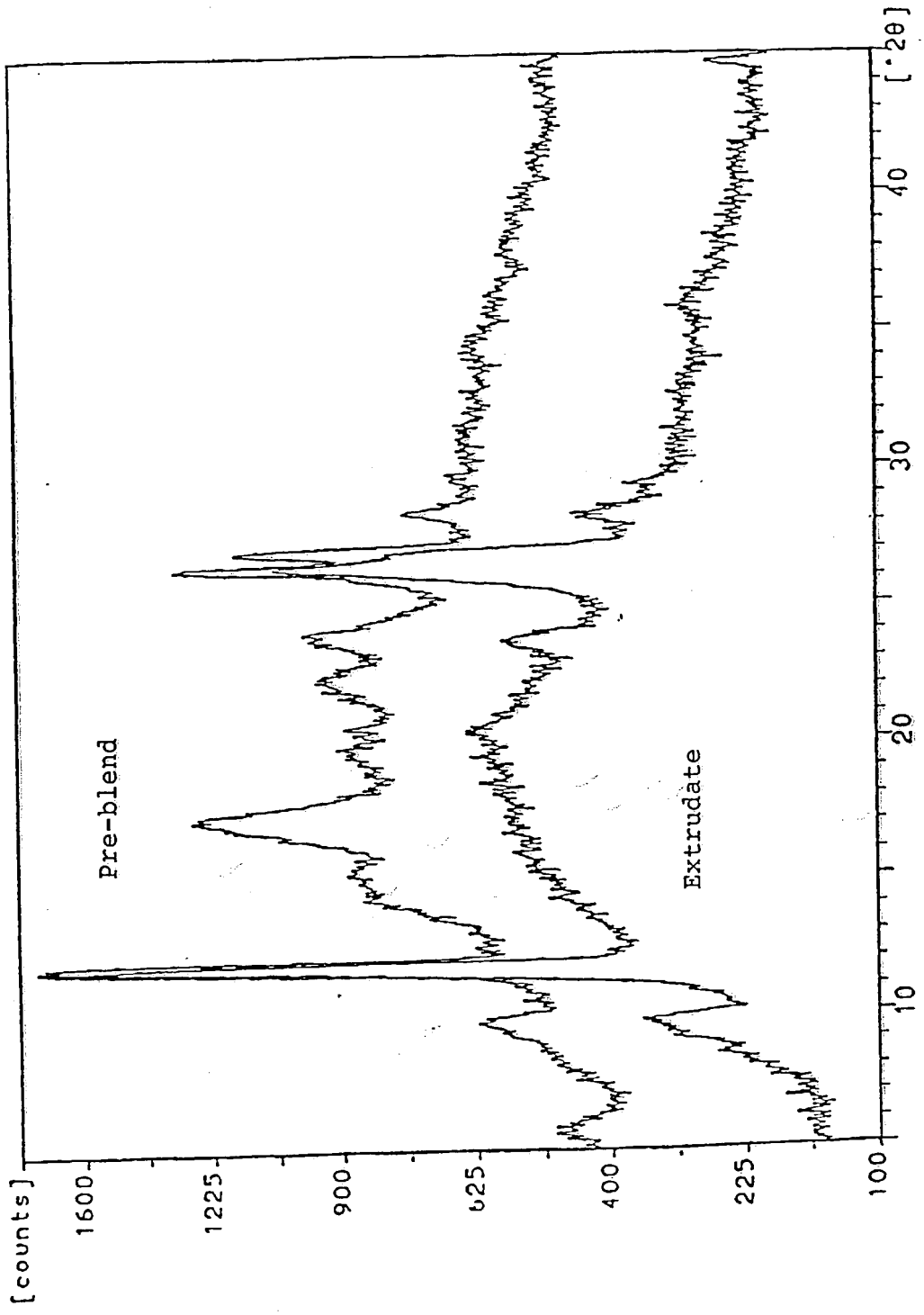
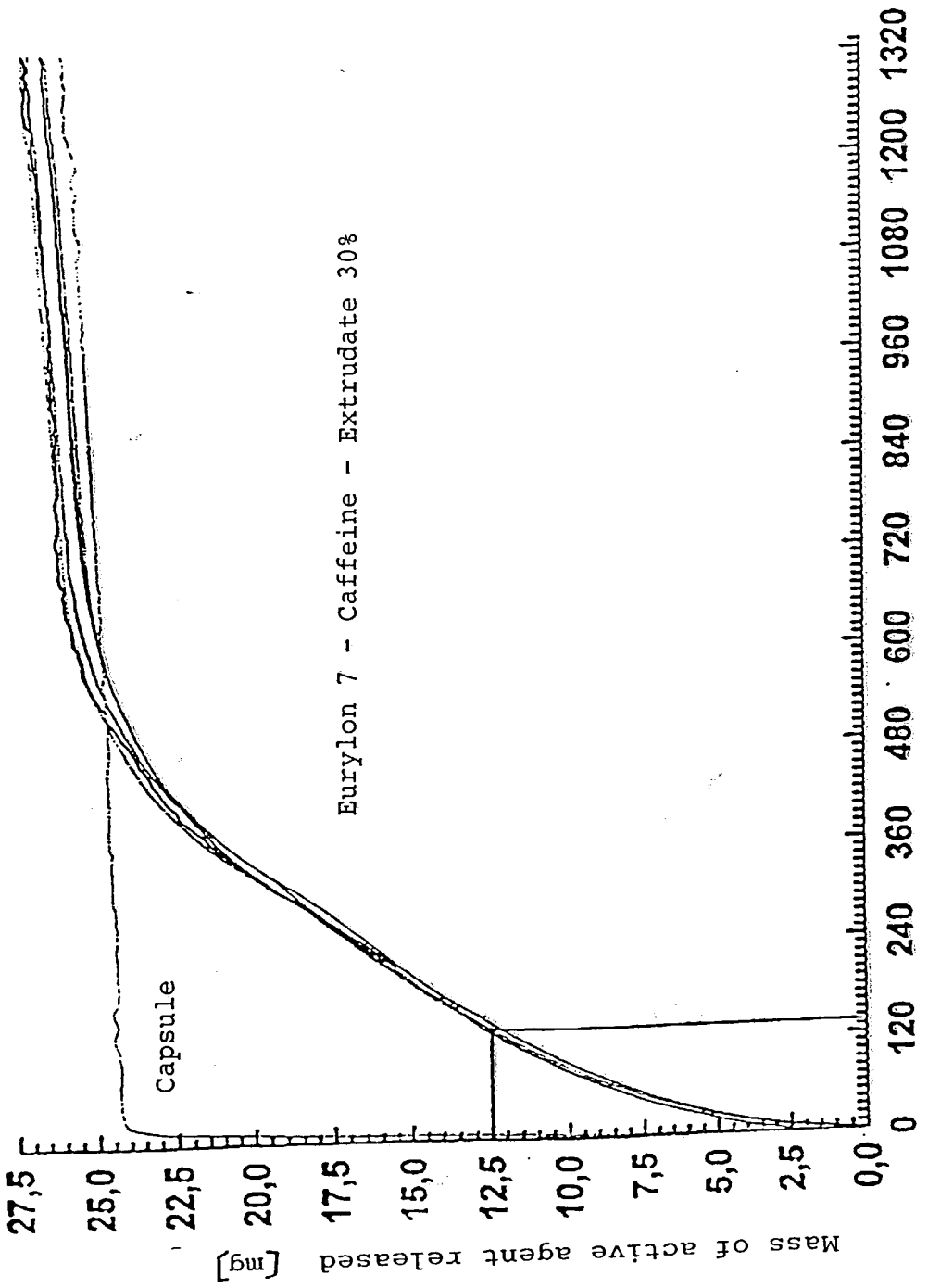


Fig. 1b

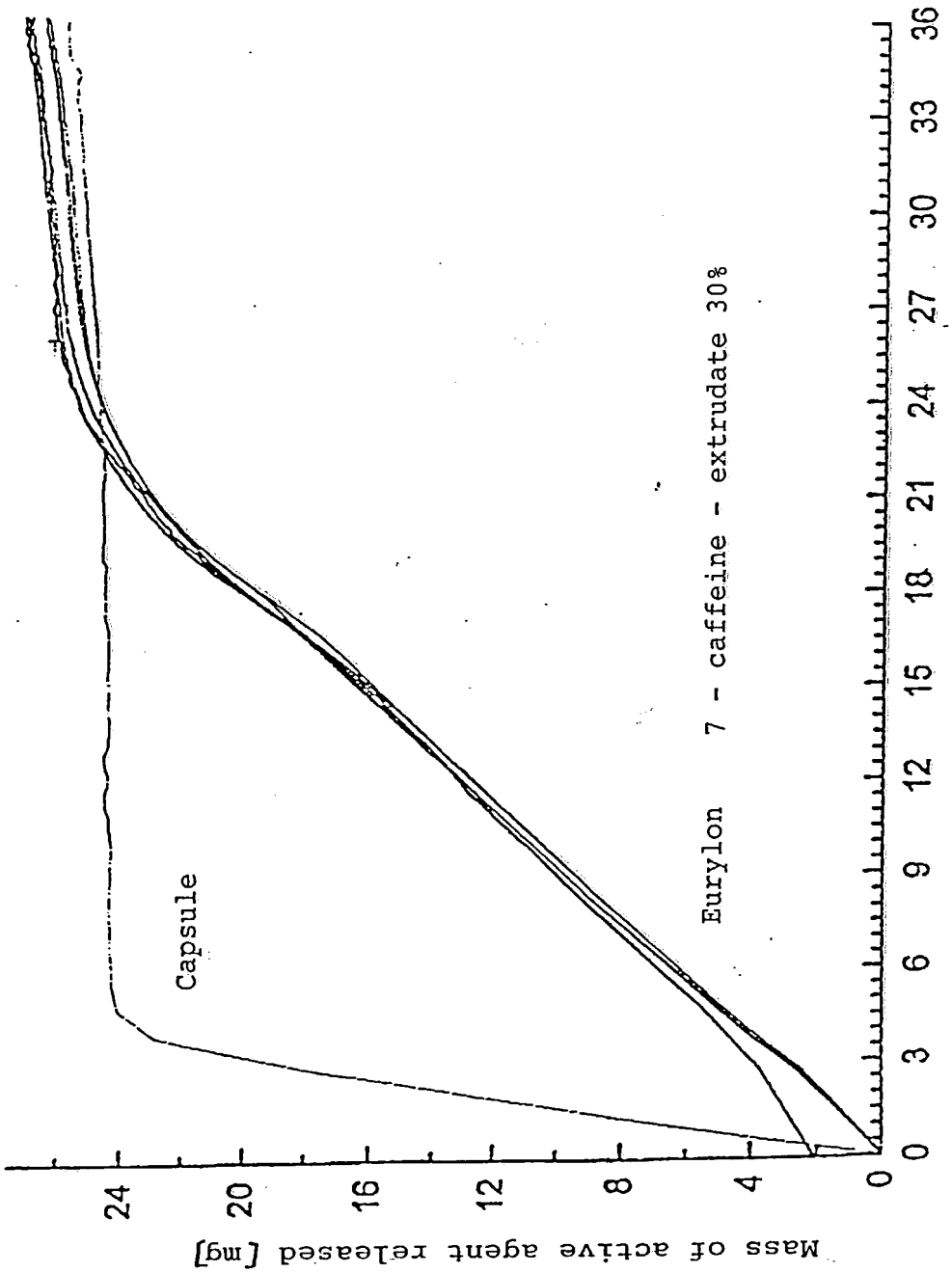
X-ray diffraction pattern of the pre-blend and the extrudate made of 80% potato starch and 20% caffeine



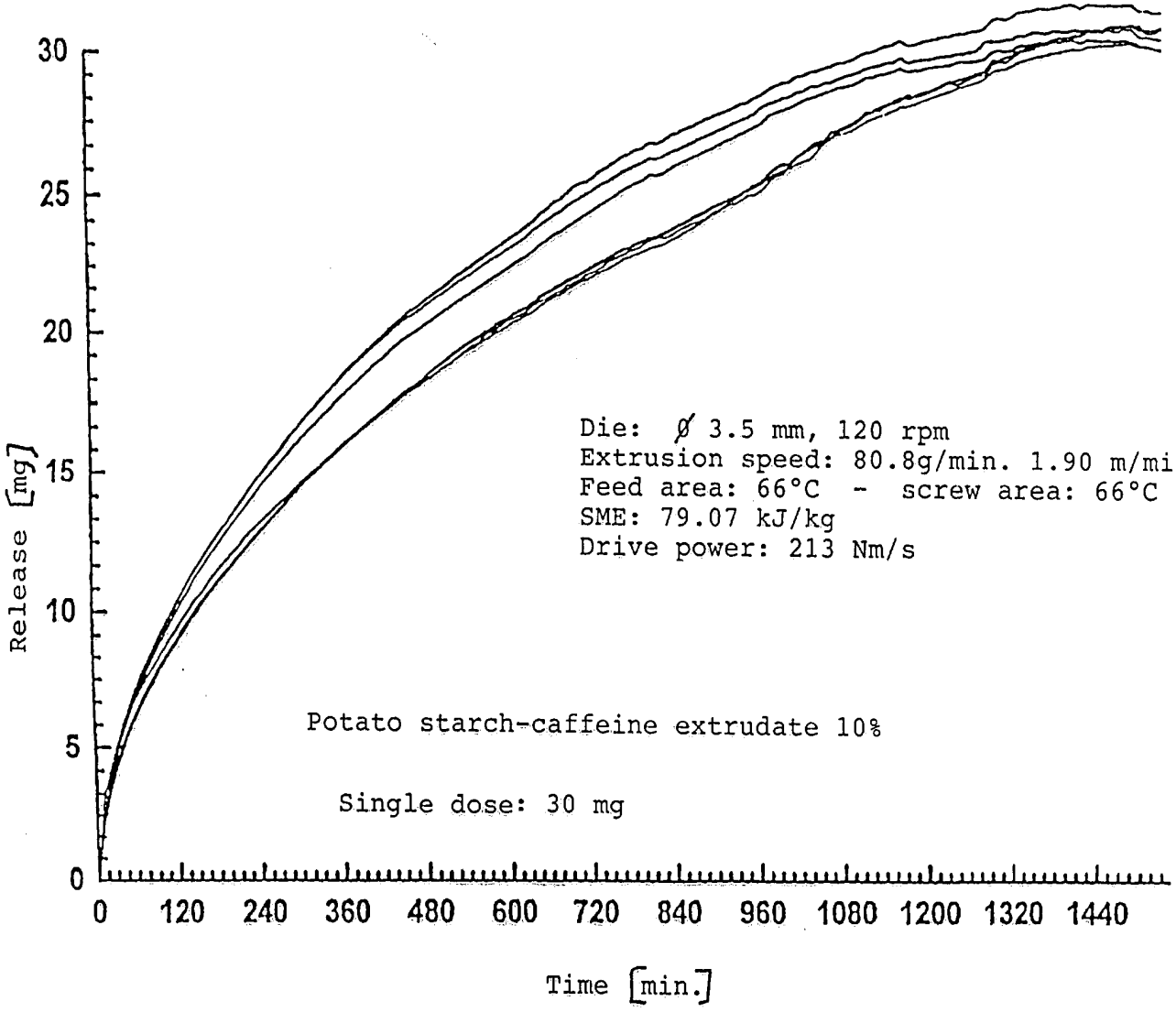
Quantitative course of active agent release of an extrudate made of Eurylon 7 and 30% caffeine

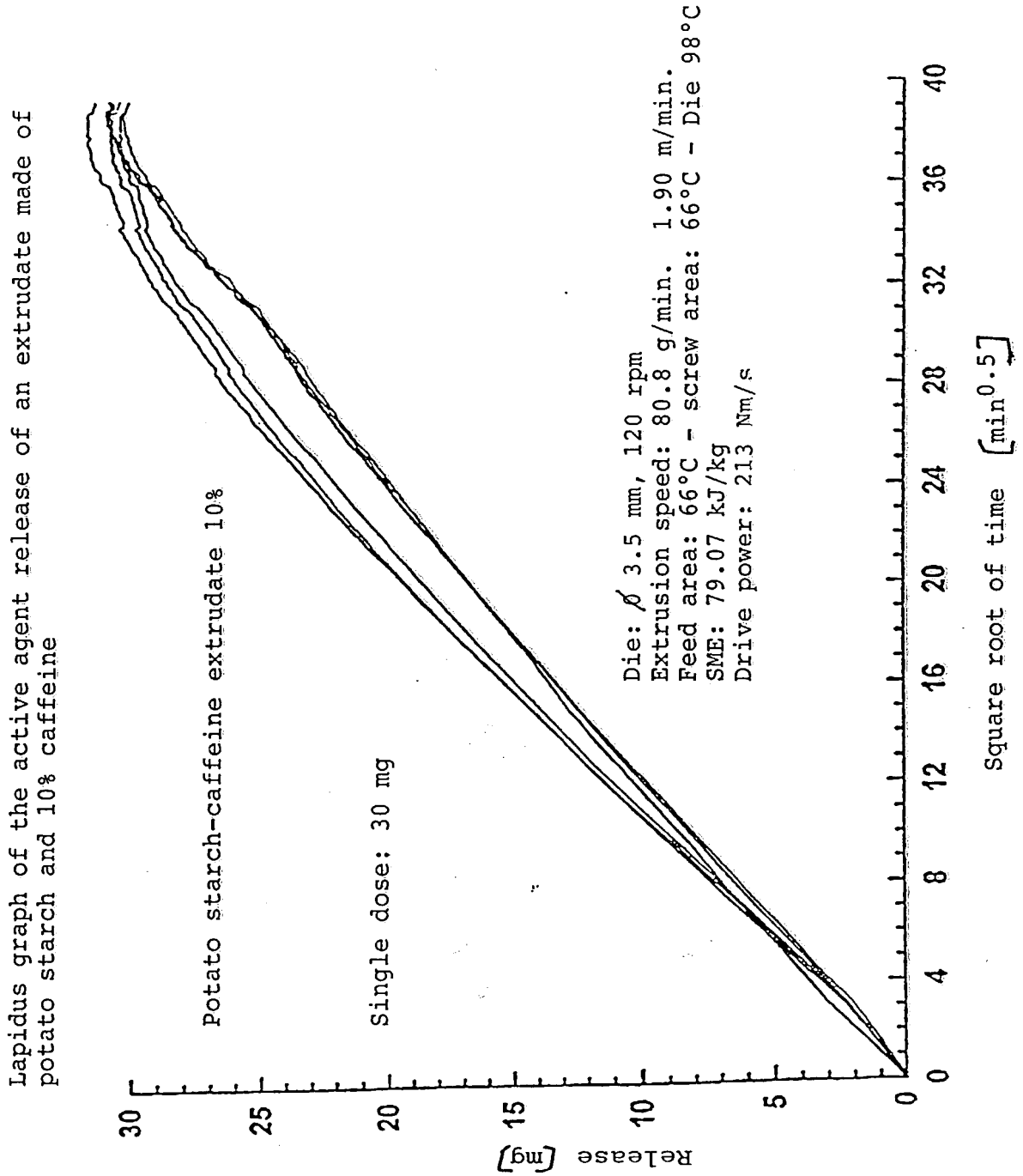


Lapidus graph of the active agent release of an extrudate made of Eurylon 7 and 30% caffeine



Quantitative course of active agent release of an extrudate made of potato starch and 10% caffeine




Lapidus graph of the active agent release of an extrudate made of potato starch and 10% caffeine
Potato starch-caffeine extrudate 10%
Single dose: 30 mg
Die: ∅ 3.5 mm, 120 rpm
Extrusion speed: 80.8 g/min. 1.90 m/min.
Feed area: 66°C - screw area: 66°C - Die 98°C
SME: 79.07 kJ/kg
Drive power: 213 Nm/s
Release [mg]
Square root of time [min^0.5]
0
5
10
15
20
25
30
0
4
8
12
16
20
24
28
32
36
40

Docket No.: 228.10.10

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **METHOD FOR PRODUCING A WATER-INSOLUBLE AMORPHOUS OR PARTIALLY AMORPHOUS CONTROLLED RELEASE MATRIX**, the specification of which (check one)

___ is attached hereto

X was filed on April 20, 2000 as Application Serial No. PCT/EP00/03612 _____ and was amended on _____ (if applicable).

X I hereby authorize and request our attorney, Davidson, Davidson & Kappel, LLC. of 485 Seventh Avenue, 14th Floor, New York, New York 10018 to insert here in parentheses (Application number _____, filed _____) the filing date and application number of said application when known.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information which is known to me to be material to the patentability of this application as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign and/or provisional application(s) for patent or inventor's certificate listed below and have also identified below any foreign and/or provisional application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR APPLICATION(S)			Priority claimed
199 18 325.2	Germany	22 April 1999	X Yes ___ No
(Number)	(Country)	(Day/Month/Year Filed)	
			Priority claimed
(Number)	(Country)	(Day/Month/Year Filed)	Yes No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial Number)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial Number)	(Filing Date)	(Status) (patented, pending, abandoned)

10

And I hereby appoint Clifford M. Davidson, Registration No. 32,728, Leslye B. Davidson, Registration No. 38,854, Cary S. Kappel, Registration No. 36,561, William C. Gehris, Registration No. 38,156, Morey B. Wildes, Registration No. 36,968, Robert J. Paradiso, Registration No. 41,240, Scott L. Appelbaum, Registration No. 41,587, Cynthia R. Moore, Registration No. 46,086, David Knasiak, Registration No. 45,991, Salvatore J. Maiorino, Registration No. 42,830, my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith; correspondence address: DAVIDSON, DAVIDSON & KAPPEL, LLC, 485 Seventh Avenue, 14th Floor, New York, New York 10018; Telephone: (212) 736-1940; Fax: (212) 736-2427.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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